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Biochemistry, Endocrinology, Human Subjects, Stress, Pituitary Hormones, Sleep and Dreaming, Biological Rhythms, Psychopharmacology	Studies accomplished under this contract included both independent studies at the Harbor-UCLA Medical Center, Torrance, CA 90509, and collaborative studies of Navy personnel conducted with the Naval Health Research Center, San Diego, CA. The focus of these studies was on the regulation of anterior pituitary hormones, both under stress conditions and under	

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conditions of neurotransmitter manipulation, and their subsequent effects on peripheral target gland hormones. Included in the studies were an acute stress study of prolactin secretion, a chronic stress study of cortisol and testosterone secretion, and the effects of dopamine receptor blockade and thyrotropin releasing hormone administration on anterior and posterior pituitary hormones.

The aforementioned studies all were done in human subjects. Some studies also were done in laboratory animals, as they could not be accomplished in humans. These included the hormonal manipulation of neonatal laboratory rats, in order to investigate the maturation of the circadian rhythms of anterior pituitary hormones and their responsiveness to stress in later life.

Finally, we also focused on the refinement of laboratory techniques, in particular developing a sensitive and gentle radioiodination method for polypeptide hormones for use in radioimmunoassay, and a quick and simple test for the suitability of these hormones for use in assays.

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FINAL REPORT

ONR CONTRACT N00014-77-C-0245<sup>red</sup>

Chemical Index to Fitness

April 1979 to September 1980

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Contract work performed at Harbor-UCLA Medical Center, Torrance, CA

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A summary of work accomplished under this contract includes the following:

The sleep-related endocrine rhythm studies conducted under our former ONR contract (N00014-73-C-0127) were completed with the data analysis and manuscript preparation of a study on hormones influencing water and electrolyte balance during sleep in normal adult men (1).

The responsiveness of the posterior pituitary hormone, arginine vasopressin, to central dopamine receptor blockade in normal adults was assessed by the administration of the dopamine blocking agent haloperidol and the serial measurement of arginine vasopressin levels in blood. Whereas prolactin secretion was considerably enhanced by haloperidol, indicating effective dopamine receptor blockade, the plasma levels of arginine vasopressin did not change significantly, suggesting the lack of a prominent dopamine neurotransmitter regulator of this posterior pituitary hormone (2).

The influence of prolactin on testosterone secretion in normal adult men was further studied by the use of methyl-thyrotropin releasing hormone to enhance prolactin secretion in normal volunteers, with serial measurement of serum testosterone levels. Methyl-TRH produced statistically significant increases in both prolactin and testosterone levels, providing further support for the concept that prolactin is a pituitary hormone capable of enhancing testosterone secretion (3).

A technique for the radioiodination of polypeptide hormones for use in radioimmunoassay was worked out, using the two enzymes glucose oxidase and lactoperoxidase. This rapid and gentle enzymatic method reproducibly results in higher yields of iodinated hormones for use in these assays (4).

A study of the maturation of the secretion patterns of the pituitary hormone, growth hormone, and the adrenal steroid, corticosterone, in neonatal laboratory rats was performed, examining the effect of hyperthyroidism as produced by thyroxine administration on the maturation of these hormone rhythms. This pharmacologic study of hormone interactions and influences on the dynamic development of circadian hormone secretion patterns was, of necessity, conducted in laboratory animals. In comparison to saline control animals, daily thyroxine administration produced a sustained elevation in basal corticosterone levels by day 12 and a significant elevation of serum corticosterone in response to stress by day 4. The serum growth hormone levels in non-stressed animals were moderately decreased in response to thyroxine administration compared to saline control animals, with a greater reduction in growth hormone measured in samples obtained from stressed animals. The results indicated that chronic thyroxine administration influences the developmental pattern of serum corticosterone and growth hormone under both non-stressed and stressed conditions (5).

A very rapid screening test (the talc-resin-TCA test) was developed to assess the suitability of radioiodinated polypeptide hormones for use in radioimmunoassays. This simple, 30 minute test

obviates the necessity of preparing a preliminary standard curve to determine the suitability of the iodinated tracer (6,7).

Experiments were performed to ascertain circadian fluctuations in the serum concentrations of luteinizing hormone, follicle stimulating hormone, prolactin, testosterone, growth hormone, thyroid stimulating hormone, and corticosterone in rats. While the serum concentrations of several of these hormones varied throughout the 24 hour period, the magnitude of change for these hormones was small compared to the range of individual hormone values at any given time point. Statistical power analysis was performed to determine the sample size necessary to reduce the possibility of a type II statistical error to an acceptable level (8).

We collaborated in a study of 8 subjects with severe phobias to small animals and insects, who were subjected to flooding therapy. Despite intense anxiety experienced by the subjects, they showed no change in plasma prolactin levels, a stress responsive hormone, in this setting (9).

A review article was prepared on hormonal regulation of renal function during sleep. This article discusses the central neurotransmitter regulation of sleep, and effects of vasopressin, aldosterone, prolactin, parathyroid hormone, catecholamines, and prostaglandins on the kidney during sleep (10).

The aforementioned studies were all done in our laboratory and in the Clinical Studies Center of Harbor-UCLA Medical Center, Torrance, CA 90509. Under this contract we also participated in collaborative studies of Navy personnel, in particular, a longitudinal stress study of 76 company commanders during basic training. Daily ratings of stress and blood sampling were performed by the Naval Health Research Center in San Diego. The blood samples have been analyzed in our laboratory for testosterone and for cortisol, the reference stress hormone. Data analysis of this study has been completed, and the manuscript of this study currently is in preparation and should be submitted for publication in the near future.

#### PAPERS PUBLISHED TO DATE SUPPORTED BY THIS CONTRACT:

1. Rubin RT, Poland RE, Gouin PR, Tower BB: Secretion of hormones influencing water and electrolyte balance (antidiuretic hormone, aldosterone, prolactin) during sleep in normal adult men. *Psychosom Med* 40:44-59, 1978.
2. Kendler KS, Weitzman RE, Rubin RT: Lack of arginine vasopressin response to central dopamine blockade in normal adults. *J Clin Endocrinol Metab* 47:204-207, 1978.
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4. Tower BB, Clark BR, Rubin RT: Preparation of  $^{125}\text{I}$  polypeptide hormones for radioimmunoassay using glucose oxidase with lactoperoxidase. *Life Sci* 21:959-966, 1977.
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6. Tower BB, Sigel MB, Rubin RT, Poland RE, VanderLaan WP: The talc-resin-TCA test: rapid screening of radioiodinated polypeptide hormones for radioimmunoassay. *Life Sci* 23:2183-2192, 1978.
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8. Poland RE, Rubin RT, Weichsel ME: Circadian patterns of rat anterior pituitary and target gland hormones in serum: Determination of the appropriate sample size by statistical power analysis. *Psychoneuroendocrinol*, 1980, in press.
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10. Rubin RT: Hormonal regulation of renal function during sleep, in Orem J, Barnes CD (Eds) Physiology During Sleep, Academic Press, New York, 1980, in press.